STORY OF DISCOVERY

Ability To Predict Type 1 Diabetes Offers Hope for Disease Prevention

Type 1 diabetes is a devastating disease that most often strikes during childhood, and invariably lasts for the rest of one's life. During every day of the lives of the millions of people with this disease worldwide, consistent attention and vigilance is required to ward off devastating diabetic complications that shorten and reduce the quality of their lives. Therefore, a key goal of NIDDK research is to develop ways to prevent type 1 diabetes from occurring in the first place. Toward realizing that goal, scientists have cleared a critical hurdle by learning how to identify people who are likely to develop the disease.

Being able to predict who will get type 1 diabetes is of obvious importance in identifying people who would benefit from prevention strategies once they are developed. But in fact it is also a key step in the development of interventions to prevent the disease. With the ability to predict type 1 diabetes risk, it becomes feasible to conduct multiple trials in those at risk, so as to increase the possibility of finding the best prevention approach. This is precisely what is being accomplished today through programs like Type 1 Diabetes TrialNet, led by NIDDK, and TRIGR (Trial to Reduce IDDM in the Genetically at Risk), led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Both programs are supported in part by the Special Statutory Funding Program for Type 1 Diabetes Research.

The scientific achievement of predicting type 1 diabetes was developed through decades of efforts by scientists in several disciplines—immunology, genetics, and epidemiology—working in several countries. Although the clinical appearance of type 1 diabetes is often sudden, with symptoms developing over weeks or days, researchers now know that the disease frequently develops gradually and silently over many years. A key advance was the ability to detect the autoimmune hallmarks of the disease prior to the actual development of type 1 diabetes. Researchers in the 1960s recognized that people with diabetes often make antibodies to insulin, a hormone produced by pancreatic beta cells that are aberrantly destroyed in type 1 diabetes, necessitating treatment with exogenously-supplied insulin. Because these antibodies often arose prior to insulin treatment, the scientists correctly surmised that the people were actually developing antibodies to the insulin being made by their own bodies. Antibodies against one's own proteins are termed "autoantibodies," and are a hallmark of autoimmune diseases like type 1 diabetes.

Indeed, researchers later discovered that people with type 1 diabetes often produce antibodies not only to insulin, but also to several other proteins produced by pancreatic beta cells. Significantly, the appearance of autoantibodies nearly always precedes the onset of overt symptoms of type 1 diabetes, when a person still has an adequate number of insulin-producing beta cells to control blood glucose. Testing for the presence of beta cell autoantibodies therefore became a promising approach to predicting the disease before its clinical appearance.

Several scientists, including NIDDK-supported researchers, worked to turn the discovery of autoantibodies into a useful tool by developing robust, standardized autoantibody tests. Importantly, they recognized that the simple presence or absence of an autoantibody does not provide as much information as accurate measurement of the levels or titer of antibody in the blood. Assays to measure antibodies can now be performed such that each test has a very low false-positive rate. Although onset of the disease

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is usually preceded by creation of antibodies to at least one of these proteins, at any given time a person destined to develop type 1 diabetes only makes autoantibodies to a variable subset of them. The presence of any one of these autoantibodies signals substantially elevated risk, and risk increases as the number of autoantibodies rises.

But type 1 diabetes is such a complex disease that, to be accurately interpreted, an autoantibody test needs to be viewed in the context of more information about the patient. It has long been known that people with a parent, brother, or sister with the disease are more likely to get type 1 diabetes than the population at large. However, most people with such relations will not get the disease, and many people without a known relative who has the disease will. The reasons for this are complex, but an important part of the answer stems from the fact that several genes turn out to predispose a person to type 1 diabetes, while several others actually have a protective effect.

The first major breakthrough in the genetic part of the puzzle came in the 1970s, with the discovery that two particular versions of a gene called *HLA*, which makes a key immune recognition protein, are much more common in people who have type 1 diabetes, suggesting they increase the likelihood of the disease. It was later discovered that certain other versions of this highly variable gene can help protect against the disease. Still other versions of HLA are more neutral in their impact. A person can acquire a high-risk version from one parent, and a protecting version from the other. The overall effect of the HLA variants accounts for a very large proportion of the genetic risk for type 1 diabetes.

With the knowledge of HLA and autoantibody associations with type 1 diabetes, NIDDK-supported scientists designed a prevention trial, the NIDDK-supported Diabetes Prevention Trial Type 1 (DPT-1), which successfully used genetic and autoantibody tests to predict risk for developing type 1 diabetes. To identify "those at risk," the researchers first selected thousands of people who have a close relative with type 1 diabetes, and then screened them for autoantibodies. Those with autoantibodies were then tested for the protective version of HLA. People who had autoantibodies and no protective HLA were tested for their response to glucose, to see whether they were already displaying signs of diabetes. Indeed, some already had the disease, and simply did not know it. The rest fell into two categories: those with a normal response to a glucose challenge were considered to have a "moderate" (26-50 percent) chance of developing type 1 diabetes within 5 years; those with a response to glucose that was weaker (but did not meet the definition of overt diabetes) were considered to have a greater than 50 percent chance of developing the disease within 5 years. Although the specific prevention strategies tested in this trial did not turn out to have a broadly protective effect, the researchers' estimates of risk for type 1 diabetes, based on their screening, proved to be remarkably accurate. Thus, the DPT-1 trial was enormously valuable in demonstrating that it is possible to identify those at high risk for type 1 diabetes—enabling researchers to conduct further studies to test new prevention strategies.

NIDDK-supported scientists are continuing to discover potential new ways to improve prediction of diabetes risk. For example, researchers recently identified another autoantibody that, when combined with tests for the previously-known autoantibodies, improves the predictive power of this approach. (Please see the advance on a new autoantibody for type 1 diabetes described earlier in this chapter.) Researchers are continuing to discover other genes that impact the probability of developing type 1 diabetes. At current count there are over 40 such genes, largely discovered through the efforts of the Type 1 Diabetes Genetics Consortium, made possible by support from NIDDK and the Special Statutory Funding Program for Type 1 Diabetes Research. Individually, none of these new genes has as large

an impact as HLA, but collectively their effect is significant.

With further genetic, autoantibody, or other predictive markers and tools, it may be possible to define risk for type 1 diabetes even more precisely, and to extend such predictive tests to the population as a whole. Such predictive markers may also help scientists identify potential environmental triggers of the disease. Improved tests to assess risk not only would facilitate additional research on prevention strategies, but could also advance research on ways to reverse the disease in its earliest stages and, importantly, enable the resulting interventions to benefit more people.